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The role of endocan and immature granulocyte in the diagnosis of acute pancreatitis

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Abstract
Aim: Acute pancreatitis is an inflammatory disease. It can progress from mild forms to serious life-threatening cases. Early diagnosis and treatment are critical for prognosis. In this study, we aimed to investigate whether serum endocan, immature granulocyte percentage (IG%) and CRP (C Reactive Protein) could be used as biomarkers in the early diagnosis of acute pancreatitis.
Material and Method: Patients diagnosed with AP (n=90) and individuals diagnosed with biliary obstruction due to choledochal stones (but not developed AP) (n=90) were included in this study. Serum endocan, IG% and CRP levels were measured
Results: Endocan, IG and CRP were found to be significantly higher in AP patients compared to controls ($p<0.0001$). According to the ROC analysis result, CRP (AUROC: 0.997) can be used to estimate AP, but endocan (AUROC: 0.638) and IG% (AUROC: 0.626) sensitivity-specificity is low
Discussion: CRP is an effective marker in the diagnosis of AP. Endocan and IG% are not effective in the diagnosis of AP because their sensitivity-specificity is low in the diagnosis of AP.

Keywords
Acute Pancreatitis, Endocan, Immature Granulocyte Percentage

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Introduction

Acute Pancreatitis (AP) is an inflammatory process of the pancreas that progresses with abdominal pain, elevated amylase and lipase [1]. Any delay in diagnosis and treatment leads to an increase in morbidity and mortality rates. Early diagnosis of AP requires a fast and reliable biomarker. Although various inflammation markers (C-reactive protein [CRP], procalcitonin, neutrophil-lymphocyte ratio [NLR]) and complex scoring systems have been developed for this purpose, there is no ideal method yet [1].

Studies have shown that endocan plays a key role in inflammation, and serum levels increase in case of inflammation [2]. Endocan levels were found to be associated with the presence and degree of inflammation and response to treatment [2].

The percentage of immature granulocyte (IG%) is a new inflammation marker that is not sufficiently known to most clinicians [3]. The detection of immature granulocytes in peripheral blood, which is not normally seen in healthy people, is an indicator of bone marrow activation and serious infection [3].

CRP is an acute phase reactant secreted against Interleukin (IL) 1 and IL-6 in the liver. CRP >150 mg/L in the first 48 hours may be helpful in the diagnosis of severe AP. In the first 48 hours (CRP>150 mg/L), the sensitivity was 80% and the specificity was 76% [4]. It is the most useful of the biochemical markers used to determine the severity and complications of AP [5].The biggest disadvantage is that the increases that occur after 72 hours are delayed and do not peak immediately after the onset of symptoms [5]. Despite this, CRP elevation in the first 48 hours is widely used because it is a cheap and reliable test that determines the severity of AP [5].

The aim of this study is to determine whether endocan and IG%, which are inflammation markers, can be used as biomarkers in the early prediction of AP severity.

Material and Methods

The study was approved by the Harran University Clinical Research Ethics Committee with the decision number HRU.22.07.27.

In this study, patients (n=90) admitted to Şanlıurfa Mehmet Akif İnan Training and Research Hospital with the diagnosis of AP between April and July 2022 and the control group (n=90) who did not have AP, who had no signs of infection in their examinations, and who were diagnosed with choledochal obstruction due to choledochal stones were included.

Blood samples were taken from patients diagnosed with AP within the first 24 hours of their admission to the hospital to measure serum endocan, IG% and CRP levels. To determine the endocan and CRP levels, blood samples were taken into serum separation tubes and centrifuged at 1000G for 15 minutes. The obtained serum samples were transferred to new tubes and stored at -80 °C until measurement. Blood samples for IG% were immediately analyzed in whole blood analysis tubes with EDTA. Blood samples in the control group were collected and analyzed similarly to the patient group.

Endocan was analyzed using the human ESM1 ELISA kit (Jiaxing, Zhejiang, China). CRP was analyzed with the Roche Cobas c 6000 instrument (Roche Diagnostics GmbH, Germany). %IG was analyzed with Sysmex XN2000 (Sysmex Inc., Japan). Endocan, IG% and CRP levels obtained from the patient and control groups were compared with the appropriate statistical method.

Statistical Analysis:

Data were evaluated using the IBM SPSS Statistics 20.0 package software (IBM, New York, USA). Data were given as number of units (n), percent (%) and mean±standard deviation. Statistical analyzes were performed using the chi-square test and the Mann-Whitney test depending on the appropriate variable. Receiver operating characteristic (ROC) analysis was performed to determine the success of endocan, IG% and CRP in predicting AP. P- value of <0.05 was considered significant. Statistical tests performed on the parameters are given in Tables 1 and 2.

Results

Of the 90 patients included in our study, 24 (26.7%) were male and 66 (73.3%) were female. The age of our patients ranged from 19 to 94 years, and the mean age was 55.67±18.94 years. Of the 90 patients in our control group, 32 (35.6%) were male and 58 (64.4%) were female. The age of our patients in our control group ranged from 20 to 94 years, and the mean age was 54.13±21.45 years.

Demographic and clinical characteristics of the groups are presented in Table 1. There was no significant difference in gender (p=0.36) and average age between the study and control groups (p=0.71).

When compared to the control group (Non AP), serum endocan, IG% and CRP levels were found to be significantly higher in the AP group (p=0,018; p=0.031, p<0,0001, respectively) (Table 1 and Figure 1).

Table 1. Comparison of demographic data, etiology, length of hospital stay and inflammation markers between the groups

	AP	Control	p-value
Number of patients (n)	90	90	
Gender (%)			
Female	73.3	64.4	0.36*
Male	26.7	35.6	
Age (years)	55.67±18.94	54.13±21.45	0.71**
Endocan (ng/L)	934.8±130.2	882.3±113.8	0,018***
Immature granulocyte percentage	0,71±0.33	0,57±0.34	0,031***
C-reactive protein (mg/L)	57,61±26.5	7,11±4.7	<0,0001***

*Fisher's exact test; **Unpaired t test; ***Mann-Whitney test; AP: Acute pancreatitis.

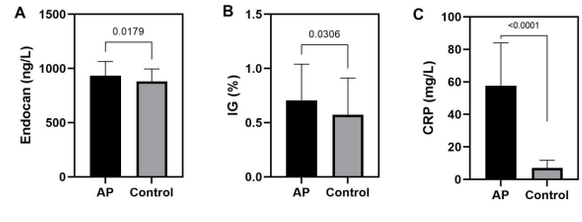

Figure 1. Endocan, IG% and CRP levels in acute pancreatitis (AP) patients and healthy controls. Data are expressed as mean ± standard deviation (sd). Data were analyzed using the Mann-Whitney test.

Table 2. ROC analysis of inflammation markers in the prediction of acute necrotizing pancreatitis

	AUROC	95% CI	Cut-off	Sensitivity %	Specificity %	p-value
Endocan (ng/L)	0,638	0.528-0.749	>872.5	57,14	69,39	0,018
IG%	0,626	0.516-0.737	>0.61	65,31	59,18	0,03
CRP (mg/L)	0,997	0.990-1.00	>23.95	100	93,88	<0,0001

AUROC: Area under ROC; CI: Confidence interval; Immature granulocyte percentage: IG%; CRP: C-reactive protein

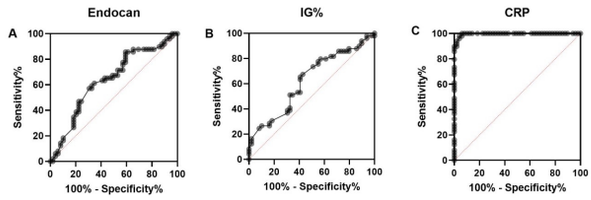

Figure 2. Receiver operating characteristic (ROC) Analysis of inflammation markers to be used in the early detection of AP. Endocan (A), IG% (B) and CRP (C)

The efficiency of endocan, IG% and CRP parameters in AP prediction was calculated using receiver operating characteristic (ROC) curves. The results obtained by comparing the areas under the ROC curve are given in Table 2 and Figure 2. According to ROC analysis results, endocan >872.5 ng/L (Sensitivity 57,14%; specificity 69.39%; p=0.018), IG >0.61% (Sensitivity 65,31%; specificity 59.18%; p=0.03) and CRP >23.95 (mg/L) (Sensitivity 100%; specificity 93.88%; p<0,0001) were determined as cut-off values for AP estimation (Table 2 and Figure 2).

Discussion

In this study, it was shown for the first time that endocan is not effective in the diagnosis of AP. It has been shown that IG% cannot be used because it is not a strong enough biomarker in the diagnosis of AP. Scoring systems and imaging methods may not provide sufficient information to determine the AP, other parameters are needed. Inflammation plays an important role in AP pathogenesis, and inflammation markers may be important in determining AP [6]. Serum pancreatic enzyme (amylase, lipase) measurements are the "gold standard" in the diagnosis of pancreatitis, but both may increase in non-pancreatitis cases; however, lipase was still found to be more specific [7]. The cutoff value for diagnosis is that these enzymes have risen more than 3 times the normal upper limit [7].

Predicting the severity of the disease plays an important role in the treatment of AP. More than 80% of AP attacks are mild, self-limited, and resolve without serious complications. Early recognition of patients is very important to prevent morbidity and mortality. It is difficult to predict which patients with AP will develop severe symptoms [7]. Scoring systems and imaging methods may not provide sufficient information to determine the severity of AP, other parameters are needed [5]. Therefore, the search for effective biomarkers in the diagnosis of AP continues.

Inflammation plays an important role in the pathophysiology of AP [8]. Endocan is a molecule involved in inflammation [2]. Therefore, we thought that endocan may be important in the diagnosis of AP. There is a limited number of studies investigating the relationship of endocan with acute pancreatitis. Baykan et al. reported in a study they conducted that serum endocan level can be diagnostic in patients with pancreatitis. [9]. In this study, serum endocan levels were found to be significantly higher in AP patients compared to the control group. This finding supports the findings of Baykan et al. However, when the AP patient and control group were compared with the ROC analysis, it was seen that endocan was not strong enough to diagnose. The sensitivity (57.14%) and specificity (69.39%) of endocan were found to be low. We think that the difference between these two studies is due to the grouping of the patients. Since, although Baykan et al. evaluated AP by dividing it into subgroups, we compared all AP patients with the control group without grouping them.

Depending on the degree of pancreatic damage and the severity of the organism's response, hepatocytes are stimulated by cytokines (IL-1 and IL-6) [4]. Accordingly, the acute phase response and the serum CRP level increase, which is the most important result of this response [10]. A serum CRP level above 150 mg/L is considered an indicator of poor prognosis [11]. The major disadvantage is that this increase in CRP peaks at 72 hours after the onset of symptoms [5]. However, CRP elevation in the first 48 hours is widely used because it is an inexpensive and reliable test that can determine disease intensity [5]. It has been reported that CRP>150 mg/L (sensitivity 80% specificity 76%) in the first 48 hours can distinguish severe AP [5, 12]. In this study, the CRP cut-off value was found to be >23.95 mg/L in the diagnosis of AP. The sensitivity (100%) and specificity (93.88%) of CRP in AP were found to be high enough to make a diagnosis. The reason for the difference between the findings obtained in this study and the previously reported findings for the CRP cut-off value is believed to be related to patient grouping. In this study, CRP data were analyzed without dividing the AP patient group into subgroups (mild, moderate, and severe AP), which is thought to be lower [12].

Immature granulocyte cells consist of promyelocyte, myelocytes, metamyelocytes and are not normally present in peripheral blood [13]. Studies show that IG can be used as an inflammation marker in the early period in the presence of inflammation [13]. More studies have been carried out recently on this parameter, which has not yet been used enough by clinicians.

The percentage of immature granulocyte (IG%) is a new inflammation marker that can be easily seen in a full blood count and is known to very few clinicians [3, 14]. Recent studies have shown that IG% relapses in the early stages of inflammation much earlier than traditional parameters such as CRP and white blood cells [3]. In the studies, it was determined that IG% of the patients in acute pancreatitis had a relapse related to the severity of the disease [3, 14]. Bedel et al. compared IG% in patients with moderate and severe AP and reported that the

IG% was higher in patients with severe AP [3]. In this study, they reported that the IG% sensitivity was low in the diagnosis of severe AP. In this study, we found that the sensitivity and specificity of IG% were too low to be used in the diagnosis of AP [3]. On the other hand, Unal et al. reported that IG% can be used in the diagnosis of acute necrotizing pancreatitis in their study by dividing AP patients into subgroups. [15]. Ünal et al. focused on patients with acute necrotizing pancreatitis. In this study, we analyzed AP patients without subgrouping them. In this way, we think that it is important in terms of revealing the general situation of IG% in AP.

Conclusion

In this study, the role of endocan in the diagnosis of AP was investigated for the first time. Endocan was not found to be a strong enough biomarker for the diagnosis of AP. Likewise, it was found that IG% was not effective in the diagnosis of AP. On the other hand, it has been seen that CRP can be used in the diagnosis of AP, as many researchers have previously reported.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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